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FILED: June 2, 1995  
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The objected to term "site near to" has been replaced with "adjacent" (page 8, line 28). This encompasses the original language "at a site near to or at the injury to or blockage" of the blood vessel.

The objected to phrase "inhibiting smooth muscle cell proliferation or restenosis of a blood vessel" has been replaced by the phrase "inhibiting mechanisms involved in restenosis" (page 5, lines 10-11). Smooth muscle cell proliferation is one component of restenosis.

The reference to blockage has been deleted since it is acknowledged that the term "injury" encompasses "blockage" as used in this context.

With regard to claims 3 and 13, the terms "gel" and "foam" have been made alternative since there is some controversy as to whether or not they are mutually exclusive. Similarly, with regard to claims 6 and 16, carbohydrates and polysaccharides have been made alternatives, to insure that those who read the claims understand that they are both intended to be encompassed. With regard to claims 8 and 18, the term "anti-inflammatories" has been deleted as duplicative. Compounds regulating the renin-angiotensin axis has been inserted in place of angiotensin and related compounds. Vitamins has been deleted as overlapping in scope.

With regard to claims 2 and 12, the surgical procedures referred to by hospitals and physicians as "peripheral bypass surgery" and "organ transplantation" are well understood. See, for example, the enclosed pages from Taber's medical dictionary. Should

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the Examiner maintain the rejection, applicants are willing to delete the reference to "peripheral" and "organ".

Claim 19 has been cancelled to facilitate prosecution.

Rejections under 35 U.S.C. §102(b) and/or §103

Claims 1-3, 5, 6, 10-16, and 19 were rejected under 35 U.S.C. §102(b) as disclosed by U.S. Patent No. 4,787,900 to Yannas. Claim 4 was rejected under §103 as obvious over Yannas. Claim 9 was rejected under §103 as obvious over Yannas in view of U.S. Patent No. 5,567,612 to Vacanti, et al. Claims 7, 8, 17 and 18 were rejected under §103 as obvious over Yannas in combination with U.S. Patent No. 5,540,928 to Edelman, U.S. Patent No. 5,455,039 to Edelman, or U.S. Patent No. 5,527,532 to Edelman in combination with Vacanti. These rejections are respectfully traversed if applied to the amended claims.

A rejection under §102 is only appropriate if each claimed element is disclosed within the bounds of a single cited reference. Yannas does not meet this requirement. The claims are not drawn to a blood vessel prosthesis, but to a matrix which is implanted **adjacent to (and typically exterior to)** a blood vessel, where the seeded endothelial cells release factors which normalize the reaction of the adjacent blood vessel to injury. Yannas is making a matrix to **recreate a blood vessel**. The intent of Yannas is to create a blood vessel, not to alter the reaction of cells endogenous to the body within blood vessels. Yannas

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insists on recreating structure; applicants seek to restore function without the need to recapitulate structure.

The independent claims have been amended to more specifically define these differences.

Yannas does not exclude the embodiment defined by claim 4, where the cells are obtained from the patient, but Yannas does not make obvious the method of claim 1, where the cells and matrix are implanted adjacent a blood vessel subjected to injury, where the result is to prevent proliferation of smooth muscle cells. In fact, Yannas teaches away from what is claimed since the entire purpose of Yannas is to encourage proliferation of the cells that are implanted to form new tissue, not affect existing tissue.

Vacanti teaches that a variety of materials can be used to make a matrix for implantation. Vacanti also teaches that one can use the matrix to deliver isolated factors released in vivo from the matrix. However, Vacanti is directed to the repair, replacement or reconstruction of genitourinary cell-matrix structures; not implantation of cells for secretion of products to inhibit smooth muscle cell proliferation.

The Edelman patents have been cited for the purpose of showing that administration of angiogenic factors or other factors affecting cellular proliferation would be obvious in view of Yannas. This ignores the teaching of Yannas, which is to recreate blood vessels, not affect the actions of the adjacent blood vessel cells, and the teachings of Edelman, which would lead one to believe that restenosis could be inhibited by

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administration of one or more compounds adjacent to a blood vessel. In combination, one would have a new blood vessel (the teaching of Yannas) with one or more active compounds released from the matrix. This would not be the same as, nor solve the problem of, restenosis. The goal of the present invention is to prevent restenosis. There was a period of time when the scientific community rather naively thought that there would be a single "magic bullet" that would stop restenosis, but clinical trials have rapidly caused a reassessment of what occurs in an individual under clinical conditions over a period of several months, versus what happens in vitro, under defined laboratory conditions. The endothelial cells on a matrix are used here as a "bioreactor" to provide many factors, since one or two simply has not been demonstrated to be effective. No art has been cited which indicates that the art recognized that many factors are required to prevent or inhibit restenosis. Moreover, no art has been cited indicating that the cells should be placed on the outside of the blood vessel, where the factors diffuse into the blood vessel.

The "all inclusive rejection" of page 7

Claims 1-19 have been rejected under 35 U.S.C. §103 on the basis of the Edelman patents in combination with Yannas, Vacanti, U.S. Patent No. 5,399,665 to Barrera, et al., or U.S. Patent No. 4,418,691 to Yannas, et al. Barrera and '691 to Yannas are addressed below. This rejection cannot be responded to for failure to identify which of the numerous prior art publications that examiner is relying on and for what purpose.

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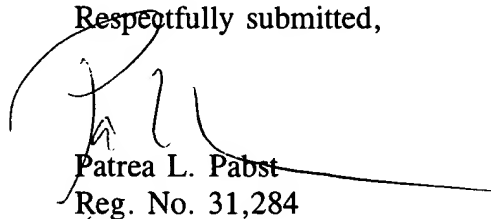
Barrera merely discloses that derivatized polymers can be prepared which have altered cell adhesion due to the incorporation of amino acids into the biodegradable polymers.

The '691 patent to Yannas discloses seeding of collagen matrices with dissociated cells for replacement of tissue. There is no selection of endothelial cells, formation of a matrix for implantation adjacent to a blood vessel, selection of a patient with an injury to a blood vessel, nor the other elements defined by the dependent claims.

Accordingly, the art alone or in combination does not make obvious the claimed method or matrix for implantation to inhibit or prevent restenosis.

Allowance of claims 1-18, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an Appendix to facilitate review by the Examiner. In the event the Examiner does not believe that the claims as amended distinguish over the art, it is respectfully requested that the undersigned and applicants be granted an interview to resolve any remaining issues.

Respectfully submitted,



Patrea L. Pabst  
Reg. No. 31,284

Dated: April 7, 1997  
Arnall Golden & Gregory LLP  
2800 One Atlantic Center  
1201 West Peachtree Street  
Atlanta, GA 30309-3450

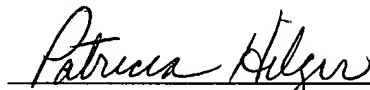
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(404) 873-8794  
(404) 873-8795 fax

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Date: April 7, 1997

  
Patricia Hilger